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Short Note

(2*S*,3*R*,6*R*)-2-[(*R*)-1-Hydroxyallyl]-4,4-dimethoxy-6-methyltetrahydro-2*H*-pyran-3-ol

Jack Bennett and Paul V. Murphy *

School of Chemistry, National University of Ireland, H91 TK33 Galway, Ireland; j.bennett5@nuigalway.ie
* Correspondence: paul.v.murphy@nuigalway.ie; Tel.: +353-91-492465

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Abstract: (2*S*,3*R*,6*R*)-2-[(*R*)-1-Hydroxyallyl]-4,4-dimethoxy-6-methyltetrahydro-2*H*-pyran-3-ol was isolated in 18% after treating the glucose derived (5*R*,6*S*,7*R*)-5,6,7-tris[(triethylsilyl)oxy]nona-1,8-dien-4-one with (1*S*)-(+)-10-camphorsulfonic acid (CSA). The one-pot formation of the title compound involved triethylsilyl (TES) removal, alkene isomerization, intramolecular conjugate addition and ketal formation. The compound was characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI mass spectrometry and IR spectroscopy. NMR spectroscopy was used to establish the product structure, including the conformation of its tetrahydropyran ring.

Keywords: glucose; tetrahydropyran; deprotection; cyclisation; functionalized scaffold

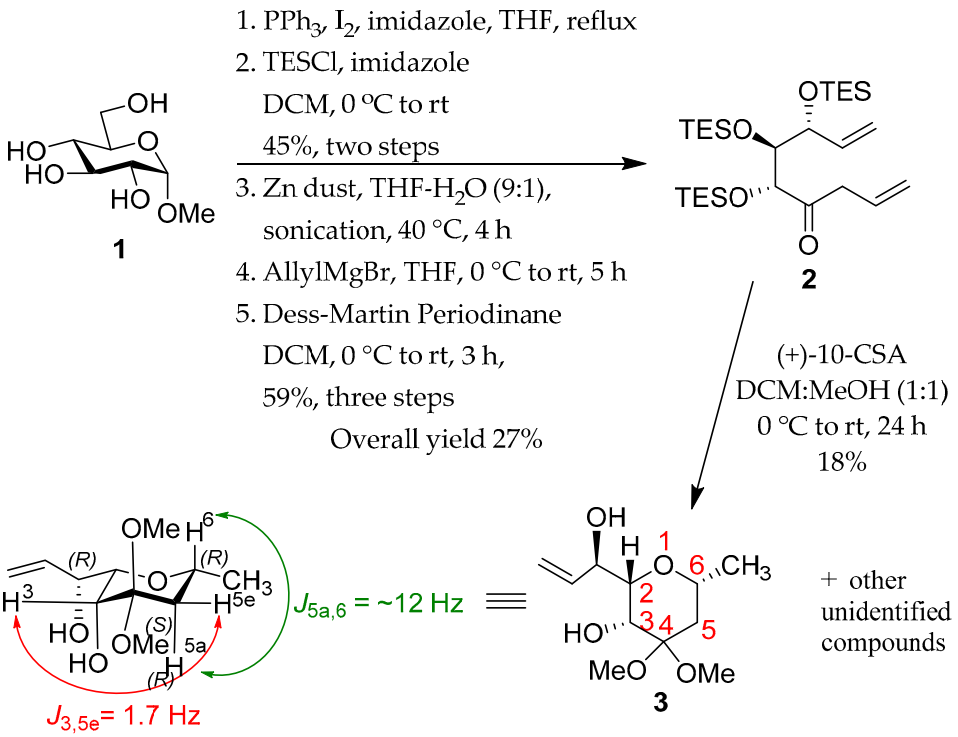
1. Introduction

Tetrahydropyran rings are found commonly in nature. Pyranoses, for example, are saccharides found in the 'glycocalyx', a carbohydrate-rich coating around cells, which is essential for interactions with biomolecules and important in numerous biological processes [1,2], including immunity, inflammation and infection [3,4]. The synthesis of mimetics of pyranoses (glycomimetics) is one strategy being investigated to give new therapies of various diseases, and this approach has received significant attention in recent years [5,6] with many structures investigated being tetrahydropyrans. The scaffolding role of pyranoses has also led to a body of work in the area of new scaffold development for medicinal chemistry [7]. Tetrahydropyrans, which are components of many secondary metabolites, have also provided inspiration for the synthesis of natural product-like compounds, leading to new hits from screening [8]. The synthesis and transformations of tetrahydropyrans has, therefore, relevance to bioactive compound discovery and development.

Herein, a chiral tetrahydropyran with various functionality is prepared from a renewable glucose derivative [9]. The product generated may serve as a scaffold or intermediate in drug discovery or chemical biology projects. The title compound may provide access to saccharide mimics or other valuable analogues of natural products, such as ratjadone, a potent antifungal [10,11].

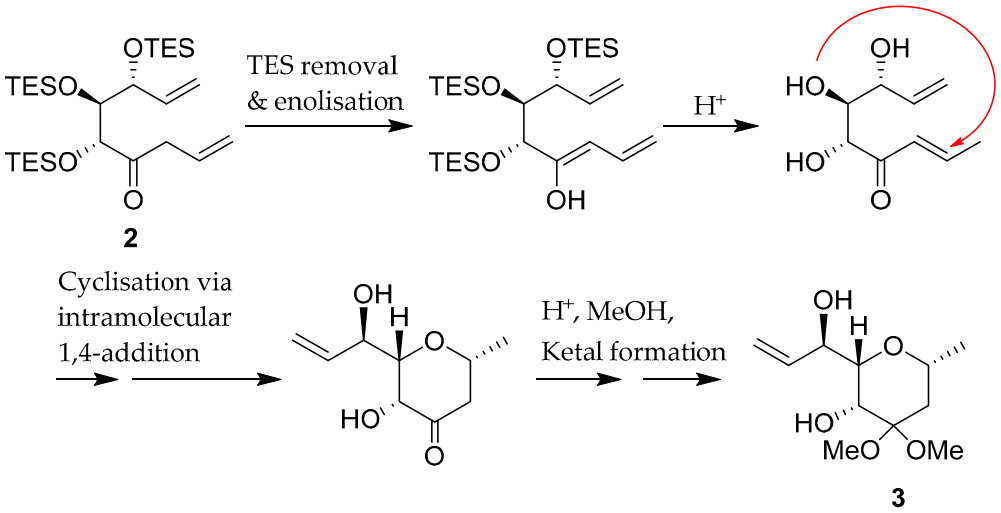
2. Results and Discussion

The work commenced from methyl α-D-glucopyranoside **1** (Scheme 1). Regioselective iodination of pyranoside **1**, followed by O-silylation and subsequent reductive fragmentation with activated zinc dust gave a TES-protected aldehyde [12,13] as a clear oil, using the procedures described previously [14–16]. Treatment of this aldehyde with allylmagnesium bromide, followed by oxidation of the resulting alcohol with Dess-Martin periodinane gave ketone **2** as a clear gel-like substance (62%). Acid-catalyzed TES removal from ketone **2** was investigated using camphorsulfonic acid [17]. Treatment of ketone **2** with camphorsulfonic acid in DCM-MeOH at 0 °C to room temperature over 24 h gave the pyran **3** as a yellow gel (18%).



Scheme 1. Synthetic route to **3**.

The tetrahydropyran derivative **3** may arise from a sequence that initially involves the removal of the TES groups, then alkene isomerization via enolisation, to an unsaturated ketone, followed by cyclisation via conjugate addition, and finally ketal formation (see Scheme 2).



Scheme 2. Proposal for the formation of **3**.

Compound **3** was isolated after chromatography of the product mixture, which contained other as yet unidentified products. To support its structure, 1D and 2D NMR spectroscopy (see Supplementary Materials), IR spectroscopy and ESI mass spectrometry were used. Analysis of the coupling constants in the ^{1}H NMR spectrum, for example, indicated the conformational and configurational assignment shown in Scheme 1. The trans-diaxial arrangement between H-5a and H-6 is supported by the observation of $^{3}J_{5e.6}$ value of 11.9 Hz. The $^{4}J_{3,5e}$ coupling of 1.9 Hz, between H-3 and H-5a, is consistent with a 'W' arrangement, which displays ^{4}J values typically <2 Hz [18].

3. Materials and Methods

All analytical data for previously reported compounds was found to be in accordance with data reported in the literature, and citations are provided. All reagents used were obtained from commercial sources and used without further purification. TLC experiments were used to monitor reactions and were performed using aluminium sheets pre-coated with silica gel 60 (HF_{254}, E. Merck, Merck KGaA, Darmstadt, Germany), with spots visualized by UV and charring with cerium (IV) molybdate, vanillin and 5% H_2SO_4 in MeOH. NMR spectra were processed and analysed using MestReNova software (*v*14.0.0-23239, https://mestrelab.com, Barcelona, Spain). Chemical shifts were reported relative to internal Me_4Si in $CDCl_3$ (δ 0.0) and CD_2HOD in CD_3OD (δ 3.31) for ^1H experiments. $CDCl_3$ (δ 77.16) and CD_3OD (δ 49.0) signals were used for ^{13}C experiments. Signals from ^1H & ^{13}C spectra were assigned using COSY, HSQC and HMBC. *J* values are reported as observed. The IR spectra were obtained using a Perkin Elmer Spectrum 100 FTIR Spectrometer. High-resolution mass spectra were obtained using a Waters LCT Premier XE Spectrometer (Etten-Leur, The Netherlands) using positive or negative mode. Chromatography was performed with silica gel 60, using petroleum ether (b.p. 40–60 °C) (PE), EtOAc, DCM and MeOH. DCM, MeOH and THF were used as obtained from a Pure-Solv™ solvent purification system.

(5R,6S,7R)-5,6,7-Tris[(triethylsilyl)oxy]nona-1,8-dien-4-one (**2**). Methyl α-D-glucopyranoside (**1**) (6.0 g, 30.9 mmol) was dissolved in THF (40 mL). PPh_3 (12.2 g, 46.3 mmol) and imidazole (4.2 g, 61.8 mmol) were added and the reaction mixture was heated to 60 °C. Iodine (11.8 g, 46.3 mmol) was dissolved in THF (5 mL) and added dropwise. The reaction was heated to reflux (75 °C) for 4 h. The reaction was cooled to rt and the salts were filtered. The residue was concentrated to dryness under reduced pressure and column chromatography using gradient elution (95:5 to 90:10 DCM-MeOH) gave the iodo-sugar (6.7 g, 73%, crude) as an orange gel. The iodo-sugar (5.5 g, 18 mmol), which contained traces of triphenylphosphine oxide, was dissolved in DCM (45 mL) under a N_2 atmosphere and cooled to 0 °C. Imidazole (7.4 g, 109 mmol) was added to the stirring solution, followed by dropwise addition of TESCl (18.3 mL, 109 mmol). The reaction was left stirring at rt for 3 h. The reaction was quenched with water and the residue was concentrated to dryness under reduced pressure. Column chromatography (elution with PE followed by a gradient from 100:1 to 60:1 PE–EtOAc) gave methyl 6-deoxy-6-iodo-2,3,4-tri-*O*-triethylsilyl-α-D-glucopyranoside (7.24 g, 62%), which had analytical data in agreement with those previously reported [12]. This intermediate (4.2 g, 6.51 mmol) was dissolved in THF–H_2O (90:10, 30 mL) and pre-activated Zn dust (4.3 g, 65.1 mmol) was added. The mixture was sonicated at 40 °C for 4 h. It was then filtered and diluted with Et_2O (20 mL). The organic layer was washed with H_2O (15 mL × 2), saturated aqueous $NaHCO_3$ (15 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure to give the intermediate aldehyde (3.0 g, 92%, crude) as a clear oil. This compound had analytical data in agreement with those previously reported [12]. This aldehyde was reacted immediately due to risk of decomposition. ^1H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, *J* 0.7 Hz, 1H, aldehyde H, H-1), 5.93 (ddd, *J* 17.1, 10.4, 7.3 Hz, 1H, H-5), 5.14 (dd, *J* 17.4, 5.9 Hz, 1H, H-6), 5.09–5.04 (m, 1H, H-6'), 4.31–4.19 (m, 1H, H-4), 3.87 (dd, *J* 5.5, 1.0 Hz, 1H, H-2), 3.74 (dd, *J* 6.5, 2.9 Hz, 1H, H-3), 1.05–0.85 (overlapping signals, 27H TES CH_3 groups), 0.60–0.46 (overlapping signals, 18H, TES CH_2 groups). HRMS (ESI) *m/z* calc for $C_{24}H_{52}O_4Si_3Na$: 511.3071; found 511.3057 $(M + Na)^+$. This aldehyde (3.0 g, 6.22 mmol) was dissolved in dry THF (10 mL) and the solution was stirred for 10 min under a N_2 atmosphere at 0 °C. Then, 1 M allylmagnesium bromide in THF (9.3 mL, 9.3 mmol) was then added slowly. The reaction was stirred at 0 °C for 10 min and was then allowed to attain room temperature and stirred for a further 5 h. Satd. aq. NH_4Cl solution was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was removed under reduced pressure to give the intermediate alcohol (3.1 g, 92%) as a clear oil. HRMS (ESI) *m/z* calc for $C_{27}H_{58}O_4Si_3Na$: 553.3541; found 553.3527 $(M + Na)^+$. This alcohol (3.1 g, 5.7 mmol) was dissolved in DCM (15 mL), Dess-Martin periodinane (4.9 g, 11.5 mmol) was added at 0 °C

and the mixture was allowed attain room temperature and then stirred for 3 h. The mixture was diluted with Et_2O (10 mL) and a 1:1 mixture of $NaHCO_3$–$Na_2S_2O_3$ (12 mL) was added and stirring was continued for 30 min. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (using a gradient mixture of 90:1 to 70:1 PE–EtOAc) gave compound **2** (2.04 g, 68%) as a clear gel like substance. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04–5.84 (overlapped signals, 2H, H-2 & H-8), 5.14 (dd, *J* 17.5, 1.7 Hz, 1H, H-9a), 5.10 (dd, *J* 10.0, 1.7 Hz, 1H, H-9b), 5.07 (dd, *J* 9.9, 1.7 Hz, 1H, H-1a), 5.02 (dd, *J* 17.2, 1.7 Hz, 1H, H-1b), 4.18 (dd, *J* 6.0, 4.0 Hz, 1H, H-7), 4.04 (d, *J* 6.3 Hz, 1H, H-5), 3.77 (dd, *J* 6.3, 4.0 Hz, 1H, H-6), 3.48 (dd, *J* 18.2, 6.9 Hz, 1H, H-3a), 3.22 (dd, *J* 18.2, 6.8 Hz, 1H, H-3b), 1.02–0.83 (overlapped signals, 27H, TES -CH_3 signals), 0.66–0.46 (overlapped signals, 18H, TES -CH_2 signals); ^{13}C NMR (125MHz, $CDCl_3$) δ 206.9 (C-4), 137.5 (C-8), 131.5 (C-2), 117.4 (C-1), 115.8 (C-9), 79.0 (C-5), 77.5 (C-6), 74.5 (C-7), 43.4 (C-3), 6.7 (TES -CH_3), 6.6 (TES -CH_3), 6.6 (TES -CH_3), 5.0 (TES -CH_2), 4.8 (TES -CH_2), 4.6 (TES -CH_2); FTIR (KBr) 2955, 2912, 2878, 1724, 1459, 1415, 1239, 1107, 1087, 1003 cm^{-1}; HRMS (ESI) *m*/*z* calc for $C_{27}H_{56}O_4Si_3Na$: 551.3384; found 551.3373 $(M + Na)^+$.

(2S,3R,6R)-2-[(R)-1-Hydroxyallyl]-4,4-dimethoxy-6-methyltetrahydro-2H-pyran-3-ol (**3**). The ketone **2** (1.2 g, 2.27 mmol) was dissolved in 1:1 DCM–MeOH (12 mL) and the mixture was stirred at 0 °C. (+)-10-CSA (2.37 g, 10.2 mmol) was added and the mixture was allowed warm to room temperature and stirred for 12 h. Multiple spots observed on the TLC suggested only partial removal of TES groups from **2** had occurred, so additional (+)-10-CSA (1.84 g, 7.94 mmol) was added and stirred for 12 h, after which a reduced number of spots indicated reaction completion. Column chromatography (using gradient elution from 98:2 to 95:5 DCM–MeOH) gave the title compound **3** (93 mg, 18%) as a yellow gel. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (ddd, *J* 17.1, 10.5, 6.7 Hz, 1H, alkene H), 5.42 (dd, *J* 17.2, 1.5 Hz, 1H, alkene H), 5.23 (dd, *J* 10.5, 1.5 Hz, 1H, alkene H), 4.34 (t, *J* 6.7 Hz, 1H, C = HC-C*H*OH), 3.64 (d, *J* 1.7 Hz, 1H, H-3), 3.58 (dqd, *J* 12.3, 6.2, 1.9 Hz, 1H, H-6), 3.39 (d, *J* 6.7 Hz, 1H, H-2), 3.22 (s, 3H, -OMe), 3.17 (s, 3H, -OMe), 2.96 (s, 1H, -OH), 2.57 (s, 1H, -OH), 1.78 (dt, *J* 14.0, 1.8 Hz, 1.8 Hz, 1H, H-5e), 1.56 (dd, *J* 14.0, 11.9 Hz, 1H, H-5a), 1.22 (d, *J* 6.2 Hz, 3H, -CH_3); ^{13}C NMR (125MHz, $CDCl_3$) δ 135.9 (alkene CH), 117.9 (alkene CH_2), 99.6 (C-4), 79.0 (C-2), 73.0 (CH_2 = CH-C*H*), 70.4 (C-6), 66.5 (C-3), 47.9 (-OMe), 47.4 (-OMe), 35.2 (C-5), 21.2 (CH_3); FTIR (KBr) 3444, 2971, 2936, 2832, 1693, 1588, 1431, 1375, 1316, 1124, 1070, 916 cm^{-1}; HRMS (ESI) *m*/*z* calc for $C_{13}H_{23}NO_5Na$ 296.1474; found 296.1463 $(M + MeCN + Na)^+$.

Supplementary Materials: The following are available online, ^{1}H and ^{13}C NMR, COSY, HSQC and HMBC spectra, optical rotation data of compounds **2** & **3** are available online.

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Conflicts of Interest: The authors declare no conflict of interest.

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